DUKE UNIVERSITY SCHOOL OF MEDICINE

Psychiatry and Behavioral Sciences
Clinical Research Unit

DATE: May 3, 2018

TO: Jan Jiang, MD, Principal Investigator
Stephen Boyle, PhD, Statistician

FROM: Sharikia Burt, MS, Assistant Research Practice Manager

RE: QA Review for Pro00009555 Responses of Myocardial Ischemia to Escitalopram Treatment

Dear Dr. Jiang,

It was a pleasure meeting with you, Stephen Boyle, PhD, and Pamela Bonner on April 19- 20th, 2018 for the abbreviated routine human subject compliance review of the aforementioned protocol performed by Department of Psychiatry and Behavioral Sciences Clinical Research Unit (CRU). The observations were noted during the QA. Please review the report and address the action items that are listed.

Objective and Scope
The review assessed adherence to Institutional Review Board (IRB) approved study protocols, Good Clinical Practices (GCP) guidelines, state and federal guidelines, protection of human research subjects, and integrity of the study data.

Methodology
At the time of the review 10 subjects were enrolled into the study. The abbreviated review included study regulatory files, 10 subject file (subjects 001-010), 10 consents (subjects 001-010), and the appropriate source documentation. The process included a review of these documents and the record contained in the eIRB. The purpose of the review is to determine if the study team has followed appropriate guidelines in the conduct of this clinical research study.

Study Synopsis

The purpose of the study is to see if a commonly used antidepressant, escitalopram (Lexapro) can improve the symptoms of mental stress induced myocardial ischemia (MSIMI). The IRB has approved enrollment for approximately 500 subjects. The study was initially approved by the IRB on 8/9/2006. At the time of the review 310 subjects were enrolled into the study. The study is currently closed to enrollment. The study remains open for continued data analysis.

Regulatory Binder:

Delegation of Authority Log:

- The delegation of authority log was re-created by Pamela Bonner starting in December 2017. It is not clear if a DOA log was created at the time of study initiation as it was not able to be located. The initials and signatures belonging to Dr. Jan Jiang, Dr. Stephen Boyle, and Pamela Bonner are entered on the log. No other initials and signatures are present. All study personnel listed on the log were assigned delegated task and approved by Dr. Jiang.
- Please note that the delegation of authority must be created at the time of the initial IRB approval and updated and maintained through study closure.

Action Items:

1. Please draft a NTF indicating that the delegation of authority log was not created at the time of the initial IRB approval and maintained during the entire duration of the study. Please alert the IRB of this occurrence by submitting a protocol deviation. Please confirm when this task has been completed.

CV's, Medical Licenses and Relevant Training:

Current signed and dated CV's were not filed in the regulatory binder for all key personnel. Current CV's have not been filed since 2008.

- Current CITI and other applicable trainings have not been filed for all key personnel. CITI and other applicable trainings have not been filed since 2007.
- Current medical licenses were not filed in the regulatory binder. Medical licenses have not been filed since 2008. Medical Licenses should be obtained and filed for each year that the key personnel is active on the study.
- At the time of the review Pamela Bonner was working to obtain current CV's, medical licenses, and relevant trainings for personnel that are listed on the DOA log.

Action Items:

- Please obtain and file current signed and dated CV's for all key personnel listed on the DOA log. If current CV's are not able to be obtained please draft and file a memo to file explaining this occurrence. CV's should be updated every two years and filed in the regulatory binder. Please confirm when this task has been completed.
- Please obtain and file current CITI and other applicable trainings for all key personnel listed on the DOA log. If trainings are not able to be obtained please draft and file a memo to file explaining this occurrence. Please confirm when this task has been completed.
- Please obtain and file current and past years medical licenses for the following key personnel listed on the DOA log:
  - Fawaz Abulaziz M Alenezi, MD
  - Kristine Arges, RN
  - Jennifer Wilson, PA
  - Angela Chambers, PA
  - Erin O'Connor, PA
  - Nicole Pristera, MD

  If licenses are not able to be obtained please draft and file a memo to file explaining this occurrence. Please confirm when this task has been completed.

IRB Approvals and Submissions:

- IRB approvals and submissions prior to the current eIRB system were filed in the regulatory binder. Whether or not all IRB approvals/submissions prior to the current eIRB system were filed was not able to be assessed. There were no IRB approvals and/or submissions from the current eIRB system filed in the regulatory binder.

Action Items:

1. Please ensure that all IRB approval letters, submissions, and approved study material are appropriately filed in the regulatory binder. Please confirm when this task has been completed.

Research Data Security Plan (RDSP):

- The approved RDSP was not located in the regulatory binder.

Action Items:

1. Please ensure that the approved RDSP is filed in the regulatory binder. Also, please ensure that all study files are stored according to the approved RDSP. Currently, the subject files are located

in a locked cabinet in the following locations at Duke South Purple Zone: Conference Room 3054, Office 3052. Files are also located on a shared drive on the S drive.

Data Safety Monitoring Board (DSMB):

- The DSMB reports were not able to be located in the regulatory binder.

Action Items:

1. Please ensure that all DSMB reports are filed in the regulatory binder. Please confirm when this task has been completed.

Package Inserts:

- The package inserts for escitalopram (Lexapro) were not filed in the regulatory binder.

ClinicalTrials.gov:

- The ClinicalTrials.gov Identifier is NCT00574847.

Action Items:

- Please ensure that the ClinicalTrials.gov documentation is filed in the regulatory binder

Action Items:

Relevant Correspondence:

- Relevant correspondence is filed in the regulatory binder. Please ensure that all relevant correspondence since IRB approval is filed. Please confirm when this task has been completed.

Subject Data and Documentation:

Subject Informed Consent Forms:

- Signed informed consents were filed in the appropriate subject folders.
- The informed consent process was not documented for any of the enrolled subjects. Informed consent notes are required to document the following:
  - Time and date of consent;
  - The informed consent was reviewed with the subject;
  - The subject had the opportunity to ask questions and all questions were sufficiently answered prior the subject providing consent;
  - The consent was signed prior to any study related procedures/activities occurring;
  - A copy of the consent was given to the subject
- It was not easily ascertained if the person who obtained consent was appropriate since the signatures on the DOA log were absent.
- The informed consents did not have two subject identifiers entered on them. For future reference, subjects that are Duke patients should have their name and medical record number entered on the upper right hand corner of every page of the consent. Subject's that are not Duke patients should have their name and date of birth entered on the upper right hand corner of every page of the consent.

Subject Data:

- Subject data located on the shared drive was not reviewed.
- There were several instances observed where source document worksheets were not fully completed. Documentation of who completed source worksheets was not consistently documented. Also, headers were not consistently entered on the worksheets.
- There were instances where visit worksheets were missing. It was not clear if the worksheets were not filed or if the visit did not occur. If the visits did not occur there was no documentation to indicate these occurrences.

- The eligibility worksheets that were present in the subject files, did not clearly indicate who completed the worksheets. There was no documentation present that indicated that subject eligibility was reviewed or acknowledged by Dr. Jiang.
- There were a number of instances PHI on subject files (i.e. medical records) were not properly redacted. PHI located on medical records should be redacted to ensure the privacy of the subjects are maintained. Per the protocol, subject names and identifying numbers will be kept on separate forms in a locked office separated from data files, and only the study coordinator and study physicians will have access to subject identities.
- There were source documents in each subject folder that were not filed according to the appropriate study visit. Some documents were filed in an unorganized manner. It was difficult to determine where these worksheets needed to be filed.
- There was a progress note dated 11/18/07 drafted for subject 006 that indicated that the subject had to stop a stress test due to PVC's. The note indicated that the subject's physician would be contacted for follow up. There was no documentation filed that indicated that the physician was contacted. Per the protocol, subjects who are unable to perform exercise testing should not be included in the study.
- It was documented that subject 005 was not able to come off beta blockers for 72 hours. The subject was able to come off the beta blockers for 24 hours. Per the protocol subjects that are unable to withdraw from anti-anginal medications during ischemic assessment phase should be excluded from the study. Per the protocol, the entire process of cardiac medication withdrawal will be monitored by the study PI and cardiology investigators. There was no documentation that indicated that monitoring of cardiac medication withdrawals occurred.
- There was documentation present for subject 004 that indicated that study medication was mailed to the patient on 11/2/07. There are no SOP's present indicating the process of mailing medication to subjects. Also, there is no documentation filed to indicate if the medication was mailed through regular mail or if courier (i.e. Fed-Ex, UPS) was used. If a courier was used, there is no tracking number present.
- The medication log was located in the study files. However, the logs were not thoroughly completed on a consistent basis.
- Although IDS orders were present in the subject files, subject randomization documentation was not present in the study files. Per the protocol, eligible subjects, who exhibit MSIMI during the screening assessments, will be randomly assigned to either escitalopram or placebo treatment. The study statistician will generate a computerized random list of numbers for assignment of study participants into one of the two arms, and the study pharmacist will prepare the study drug and the placebo into identical appearing capsules that will be contained in bottles identified by code numbers.

Action Items:

1. Please confirm the process for gaining access to all data on the secure server if an audit were to occur.
2. Please ensure that all subject source documents are filed appropriately and in an organized manner.
3. It is recommended that eligibility checklists are utilized to aid researchers in assessing and documenting the eligibility of each study subject screened for inclusion into the study. Please note that, all subject files must include supporting documentation to confirm subject eligibility. The PI along with the study personnel delegated to assess eligibility should sign the checklist.
4. Please redact all PHI from medical records that are present in the subject files. Please ensure all records are stored according to the protocol and RDSP.
5. Please ensure all headers on the source document worksheets are completed.
6. It was documented that subject 005 was not able to come off beta blockers for 72 hours. The subject was able to come off the beta blockers for 24 hours. Please confirm if this subject was suitable to be enrolled in the study. Per the protocol subjects that are unable to withdraw from anti-anginal medications during ischemic assessment phase should be excluded from the study. Per the protocol, the entire process of cardiac medication withdrawal will be monitored by the

study PI and cardiology investigators. Documentation that the monitoring of medication withdrawal was not found in the subject files. Please indicate if this documentation exist.

7. There was a progress note dated 11/18/07 drafted for subject 006 that indicated that the subject had to stop a stress test due to PVC's. The note indicated that the subject's physician would be contacted for follow up. There was no documentation filed that indicated that the physician was contacted. Per the protocol, subjects who are unable to perform exercise testing should not be included in the study. Please confirm if the subject was suitable for enrollment into the study.
8. Please ensure that all subject files are complete. Any data that is entered on the worksheets after the study visit should clearly be designated as a late entry, initialed and dated at the time of entry. If data is not able to be obtained, a note to file should be drafted explaining the occurrence. If appropriate, missing data should be reported to the IRB as a deviation.
9. Please clarify if mailing study medication was allowed. Please indicate if there are SOP's that outlined the procedure for mailing medication to study subjects. If study medication was mailed to subjects using a courier, please provide tracking numbers.
10. Medication Count Logs were present in subject files. Medication Count Logs were not fully completed. Please confirm if the Medication Count Logs were used as drug accountability logs. If not, please clarify where drug accountability logs are located.
11. Please confirm where the subject randomization records are located.

Enrollment Log:

- Pamela Bonner provided the enrollment log via email on 4/18/18.
- All subjects were not entered on the enrollment log.
- All data fields were not completed on the enrollment log.
- The enrollment log did not consistently include stop dates, reason and/or date of dropouts or withdrawal for subjects that were enrolled in the study.

Action Items:

1. Please ensure that all data is entered on the enrollment log. Please confirm when this task has been completed.

Adverse Events/Serious Adverse Events (AE/SAE's)

- There were several instances observed where AE's were documented on the treatment phase study worksheets or progress notes in the subject files, however the AE's were not thoroughly documented, assessed, or followed up by the study team. An AE log was not present. Documentation of the AE's start date, stop date, causality, severity, seriousness, outcome, action taken with study drug, and PI acknowledgement was not present in the study files. Although not documented in the source documents, Dr. Jiang indicated that she reviewed and assessed AE's during the course of the study.
- Adverse Events were documented on the long term follow up worksheets.
- Documentation of SAE's were not present at the time of the review.

Action Items:

1. Please submit a deviation to the IRB indicating that AE's were not properly documented and assessed during the course of the study. Please confirm when this task has been completed.
2. All adverse events and serious adverse events must be documented and followed up on by the appropriate study personnel. Please refer to the Duke IRB website (https://irb.duhs.duke.edu/irb-review-process/faqs/reporting-irb) for reporting requirements for AE's and SAE's.

Protocol Deviations/Violations:

- At the time of the review there were no protocol deviations/violations documented by the study team. It is the responsibility of the PI and study team to report it to the IRB and to implement appropriate corrective/preventative actions.
- It is recommended to create a log to capture and track protocol deviations/violations.

Please refer to the Duke IRB website (https://irb.duhs.duke.edu/irb-review-process/faqs/reporting-irb) for reporting requirements for protocol deviations/violations.

Miscellaneous:

- In order to ensure data integrity, validity, and subject safety data should always be Attributable, Legible, Contemporaneous, Original, and Accurate (ALCOA) for the proper verification of source documents.

- There were several instances where source document worksheets were completed with purple ink or pencil.
- There were several instances where errors were not corrected appropriately.

Miscellaneous Action Items:

1. Please ensure that black or blue ink is used when consenting subjects and completing source documents worksheets.
2. Please ensure that errors are corrected by inserting a single line through the error and initialing and dating the correction. Errors should not be obliterated.
3. Please ensure memo to files include the following: Protocol ID, Date, Subject of memo, Explanation of the Issue, Corrective/Preventative Actions (if applicable), Signature of individual drafting memo, and PI signature (if applicable).

Due to the various issues observed during the QA review that may affect data integrity, subject safety and the concern for proper PI oversight it is my recommendation that the study be escalated to Duke's Office of Audit, Risk, and Compliance (OARC). This has been discussed with Dr. Jan Jiang (PI) along with the Dr. Moira Rynn (Department of Psychiatry Chair).

Thank you for providing me the opportunity to review your study files and to provide feedback. If you have any questions or concerns in regards to this QA review, please feel free to let me know.

Kind regards,

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